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CRITICAL REVIEW

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# Is Indirect Exposure a Significant Contributor to the Burden of Perfluorinated Acids Observed in Humans?

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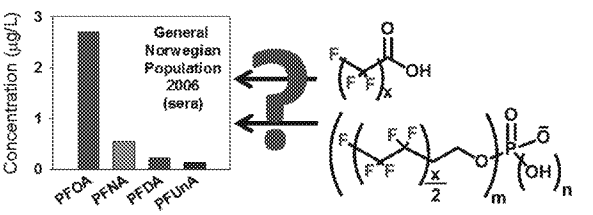
Supporting Information

ABSTRACT: In comparison to other persistent organic pollutants, human fluorochemical contamination is relatively complicated. This complication arises at least in part from a disparity between the chemicals used commercially and those measured in the environment and humans. Commercial fluorochemical products are dominated by fluorinated polymers used in textile or carpet applications, or fluorosurfactants used in applications ranging from personal care products, leveling and wetting agents, to greaseproofing food-contact materials.




Investigations into environmental and human fluorochemical contamination have focused on perfluorinated acids (PFAs), either the perfluorinated carboxylates (PFCAs) or sulfonates (PFSAs). In this review we will present an overview of data related to human fluorochemical exposure including a discussion of fluorochemical production, concentrations in exposure media, biotransformation processes producing PFAs, and trends in human sera. These data will be presented in the context of how they can inform sources of human PFA contamination, specifically whether the contamination results from direct PFA exposure or indirect exposure via the biotransformation of commercial fluorochemicals or their residuals. Concentrations of both perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) began to decrease in human sera around the year 2000, a change that mirrored the 2000−2002 phase-out of perfluorooctane sulfonyl fluoride (POSF) production. These temporal trends suggest exposure to current-use POSF-based materials was a significant source of PFOA and PFOS exposure prior to 2000. Relatively slow PFOA elimination and increasing concentrations of the C9 and C10 PFCAs in human sera suggest continued PFCA exposure, without similar exposure to PFOS, which is consistent with indirect exposure via the biotransformation of fluorotelomer-based materials. Conversely, human exposure models have suggested direct exposure to PFAs present in food items is the major source of human contamination. The data set presented here cannot unequivocally delineate between direct and indirect human exposure, however temporal trends in human sera and exposure media are consistent with indirect exposure representing a significant portion of observed human PFA contamination.

## INTRODUCTION

Polychlorinated biphenyls (PCBs) or polybrominated diphenyl ethers (PBDEs) are used commercially and observed in the same form within the human body.[1,2] Determining the major sources of PCB or PDBE human contamination then involves budgeting exposure pathways by determining concentrations in exposure media and consumption patterns.[1,2] This is not a simple task. However. for human fluorochemical exposure the issue is complicated by the fact that the perfluorinated acids (PFAs) (either the perfluorinated carboxylates (PFCAs) or sulfonates (PFSAs)) measured in human sera have limited commercial applications,[3−5] and it is possible that degradation of commercial fluorochemicals may be a source of the observed PFA contamination.[6,7] The situation is compounded by the variety of commercial fluorochemicals produced and their diverse applications. Therefore, accurate modeling of human indirect exposure to commercial fluorochemicals would involve concentration data in relevant exposure media as well as specific migration, uptake, excretion, and transformation estimates. This is a monumental task, which is particularly challenging given the limited data available publically regarding the use of commercial fluorochemicals in various applications.

Given the breadth of commercial fluorochemicals produced and their various applications, it is difficult to obtain comprehensive data sets in exposure media. We do however have strong data sets for PFA concentrations in human sera.[8−19] These data sets have been generated by several laboratories around the world, with relatively consistent results. We will present temporal data on human fluorochemical contamination in the context of how it can inform sources of human exposure. In addition to discussing direct versus indirect exposure we are also interested in delineating between exposure to legacy environmental contamination versus current-use commercial materials.

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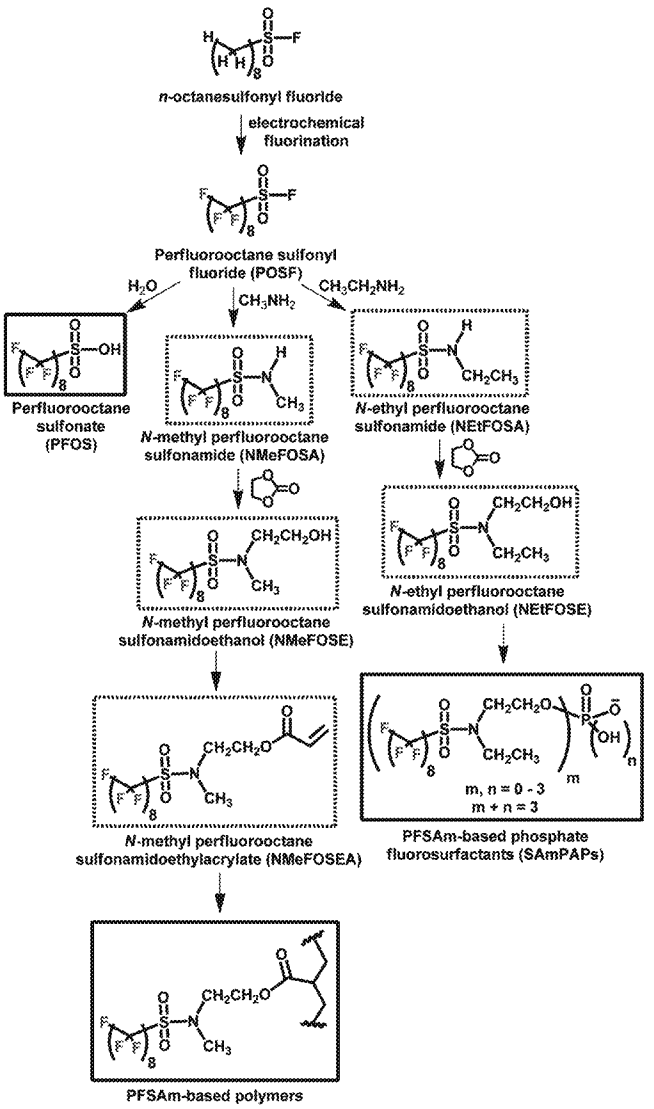


**Figure 1.** Manufacturing scheme for the production of the perfluorinated sulfonamide (PFSAm) commercial products via electrochemical fluorination (ECF). Commercial products are identified by solid boxes and known residual materials are identified by dashed boxes.[3,4]

## FLUOROCHEMICAL PRODUCTION AND TRENDS IN MANUFACTURING

Fluorinated materials are produced via two major manufacturing processes: electrochemical fluorination (ECF) and telomerization.[3] ECF replaces hydrocarbon hydrogens with fluorines via electrolysis in hydrogen fluoride.[3] The major ECF product was perfluorooctane sulfonyl fluoride (POSF) with about 20% structural isomer[4,20] (Figure 1). Using either methylamine or ethylamine POSF was used to produce *N*-methyl or *N*-ethyl perfluorooctane sulphonamide (NMeFOSA or NEtFOSA), respectively, which were functionalized with ethylene glycol to produce *N*-methyl or *N*-ethyl perfluorooctane sulfonamidoethanol (NMeFOSE or NEtFOSE). These alcohols were the building blocks for the perfluorinated sulfonamide (PFSAm)-based commercial products. NMeFOSE was incorporated into polymeric materials used in textile and carpet applications, whereas NEtFOSE was incorporated into phosphate surfactants (SAmPAPs) used in paper food packaging.[4,11] Perfluorohexane sulfonyl fluoride (PHxSF) was a contaminant of the POSF feedstock and the resulting commercial materials, as well as a building block for certain fire-fighting foams and carpet treatments.[10,21]

Telomerization produces fluorinated chemicals by iterative reaction of perfluoroethyl iodide (telogen) with perfluoroethylene (taxogen) (Figure 2), producing perfluoroalkyl chains that differ in length by $CF_2CF_2$. Iodine atom transfer yields a mixture of linear perfluorinated iodides.[3,5] Reaction with ethylene produces fluorotelomer iodides (x:2 FTI), which can be hydrolyzed to produce fluorotelomer alcohols (x:2 FTOH). Commercial fluorotelomer products can be manufactured from FTIs, FTOHs, or the fluorotelomer olefins (x:2 FTOs), which are produced by treating FTOHs with a strong base.[3,5] Fluorotelomer-based polymers are produced by functionalizing the FTOHs to a fluorotelomer acrylate (x:2 FTAc) for incorporation into the polymer structure.[3,5] In 2004, 80% of fluorotelomer-based commercial products were polymeric materials applied to carpets and textiles, with the remaining 20% used to produce fluorosurfactants used in a variety of applications including personal care products, leveling and wetting agents, and food-contact packaging.[22] The perfluorooctyl chain length was preferred in polymeric materials, and the perfluorohexyl chain length in surfactants.[23] However, despite optimization, a range of perfluorinated chain lengths (C2 to C18) are produced and carried through to the final product.[24]

Yields for the reactions shown in Figures 1 and 2 were not 100%, and significant concentrations (0.04−3.8%) of unreacted starting materials can be detected in the final commercial products.[25] These starting materials are often referred to as *residuals* or *PFA precursors*, as studies have generally shown the hydrocarbon moieties are consumed until only the recalcitrant PFSA or PFCA remains.[26−34] However, as the commercial products themselves can also be transformed into PFAs,[7,35] we will use the term residual to refer specifically to these unreacted starting materials.

Trends in fluorochemical production are shown in Figure 3A. 3M was the major manufacturer of the POSF- and PFHxS-based materials. POSF production began in 1949 and continued until these materials were phased out between 2000 and 2002.[36,37] 3M has since returned to the market with perfluorobutyl-based materials.[37] At its peak in the late 1990s the global production of POSF-based materials was estimated at 4650 tonnes per year.[4] Although POSF-based materials are now regulated in the United States[38] and Europe,[39] production continues in Asia (www.haixinfluoride.com/eproducts.html) with little publically available data regarding the magnitude of this production.[10] PHxSF-production was also phased out with POSF in favor of the perfluorobutyl chemistries.[37] Since the POSF phase-out, fluorotelomer production has continued to increase, reaching 12 000 tonnes annually in 2004.[22,23] At the same time, residual FTOHs are likely decreasing due to a voluntary stewardship program established in 2006 with the U.S. Environmental Protection Agency to reduce residual FTOHs by 95% by 2010 and 100% by 2015 (www.epa.gov/oppt/pfoa/).

PFAs have some direct commercial applications. Perfluorooctane sulfonate (PFOS) was used in aqueous film forming foams (AFFF), semiconductors, hydraulic fluids, and photolithography.[4,40−42] These applications are being phased out in Europe,[4,40−42] and are controlled in the United States.[38] Perfluorooctanoic acid (PFOA) is not known to have any direct commercial applications, but is used as a processing aid in the manufacture of fluoropolymers, specifically polytetrafluoroethylene (PTFE), which is the functional component of nonstick pans. PFOA exposure through the use of

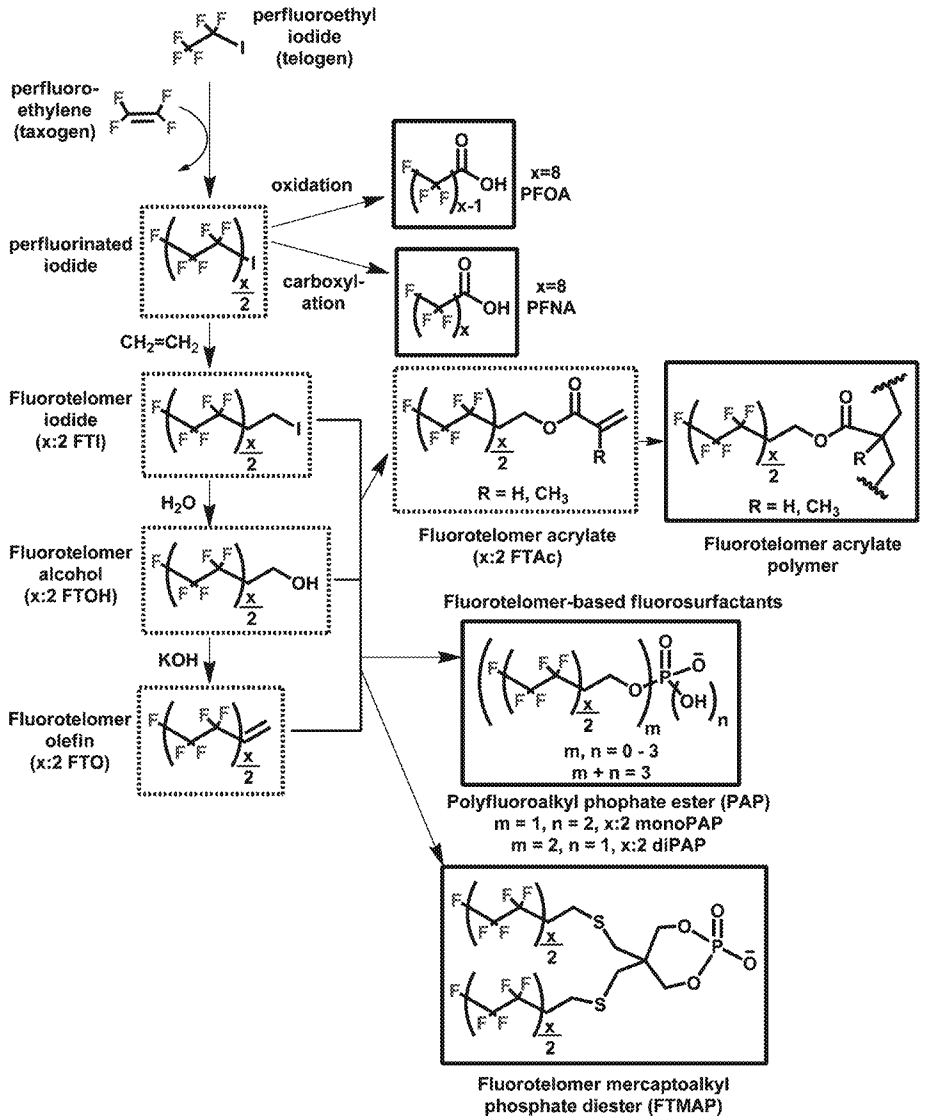


**Figure 2.** Manufacturing scheme for the production of fluorotelomer commercial products via telomerization. Commercial products are identified by solid boxes and known residual materials are identified by dashed boxes.[3,5]

PTFE-coated pans is insignificant,[43,44] likely because PFOA is not thermally stable at the temperatures used in the manufacture of these products. Before 2002 PFOA was largely produced by ECF (via fluorination of *n*-octanecarbonyl fluoride); since 2002 the production of PFOA has likely been fluorotelomer-based.[4,11] Perfluorononanoic acid (PFNA) also has limited commercial applications, mostly in Japan.[5]

## HUMAN PFA CONTAMINATION AND EXPOSURE MODELING

Human PFA exposure can occur via exposure to the PFA itself (direct PFA exposure) or via exposure to a residual or commercial fluorochemical with subsequent biotransformation (indirect PFA exposure). In this discussion, direct and indirect will be defined with respect to human exposure not industrial production. We are using this definition as these direct and indirect pathways of human exposure are distinct with respect to the associated toxicology, relevant exposure media, observed intermediates, and the resulting PFCA congener profile.

All human exposure models to date have suggested direct exposure to PFAs present in food items is the dominant source of human contamination, with some contribution from dust to young children.[45−50] This result is consistent among those studies that consider direct PFA sources only[45−47] as well as those that consider both direct and indirect sources.[48−50] However, these studies do not compare the results of these exposure models with the temporal data sets available in human sera.[11,15−19] Temporal trends in human sera for select PFSAs and PFCAs are plotted in Figure 3B together with the arithmetic human serum elimination half-lives for PFHxS (8.5 years), PFOS (5.4 years), and PFOA (3.8 years).[51] Using the values from Haug et al.[19] after the year 2000 and assuming depuration beginning in either 2000, 2001, or 2002 results in elimination kinetics that range from 3.5 to 4.6 years for PFOS and 6.2 to 13 years for PFHxS (see Supporting Information (SI)). These half-lives are similar to their literature elimination half-lives and suggest the major source of exposure was removed with the POSF phase-out (Figure 3A). Contrary to the temporal changes observed in human sera, PFA contamination present in Canadian food items remained the same

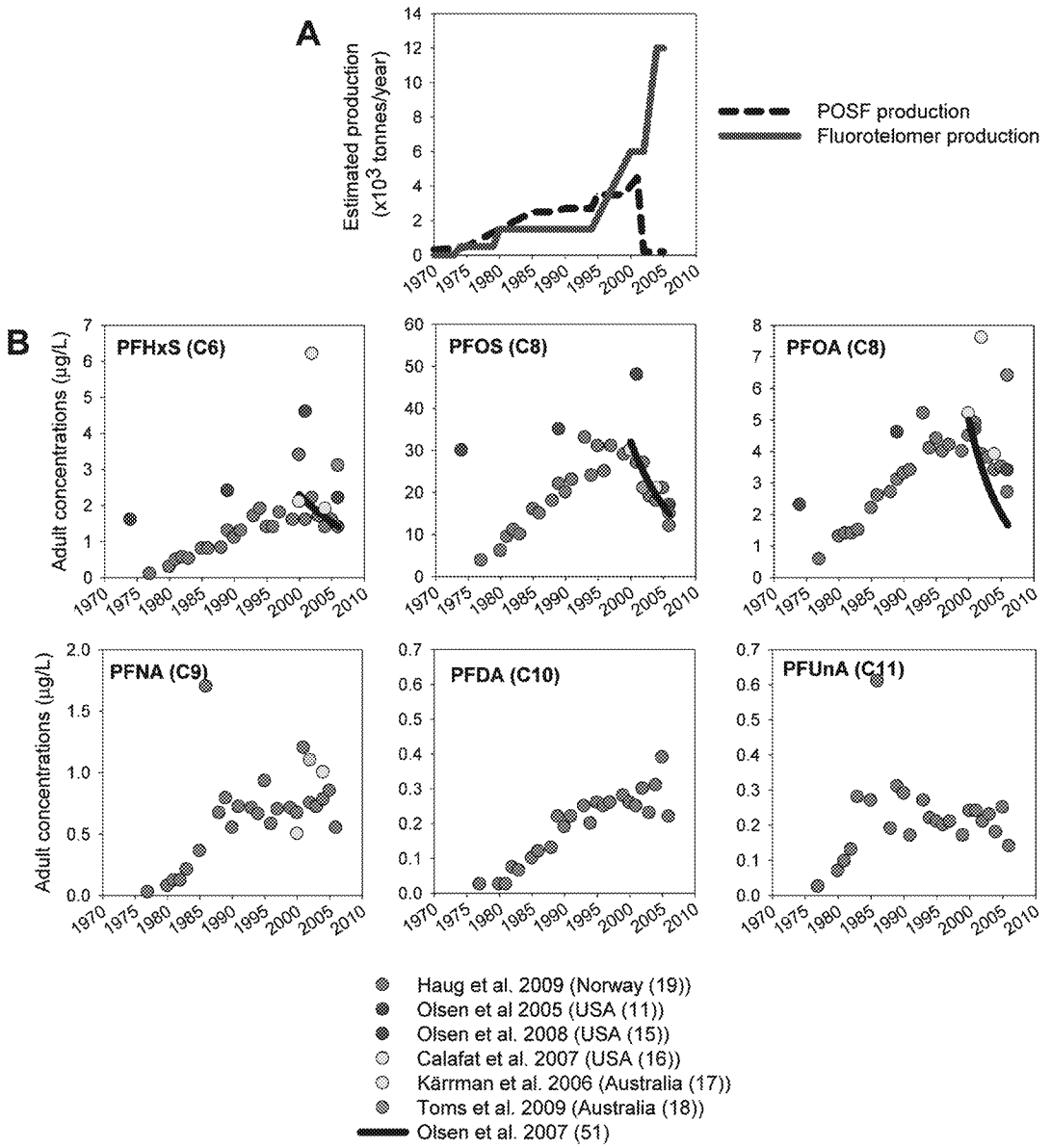


**Figure 3.** (A) North American and European POSF and fluorotelomer production values from 1970 to 2020.[8,23] (B) Temporal trends in human sera[11,15−19] plotted with the arithmetic human serum elimination half-lives for PFOS (5.4 years), PFHxS (8.5 years), and PFOA (3.8 years).[51]

or increased between 1998 and 2004.[52] Disparity between contamination trends in human sera and food suggest food items were not the major source of human exposure to PFHxS and PFOS before the 2000−2002 POSF phase-out. That PFHxS and PFOS levels in human sera responded so quickly to a change in chemical production suggests current-use commercial materials or their residuals were likely a major source of exposure, and not legacy environmental contamination such as that present in food.[8,46] This being said once PFHxS and PFOS from POSF-related sources are depurated, contamination present in food items could be the dominant exposure pathway.

Similar to PFHxS and PFOS, PFOA concentrations in human sera began to decline around the year 2000. However, unlike the plots for PFHxS and PFOS, PFOA elimination was slower (7.1−8.5 years (see SI[19])) than its literature half-life of 3.8 years.[51] This suggests POSF production may have been a source of human PFOA exposure prior to the 2000−2002 POSF phase-out, but that exposure to PFOA continues through a source unrelated to POSF. How POSF production was related to human PFOA exposure is not clear. There is limited evidence to suggest PFOA may be produced from NEtFOSE microbial degradation,[10,53] although PFOA was not observed in a separate study with a similar experimental setup.[26] It is also possible human PFOA exposure may have decreased in response to changes made by other fluorochemical manufacturers around the same time period, although estimates from fluorotelomer manufacturers suggest overall production continued to increase (Figure 3A).

A recent review article of human PFCA contamination by Vestergren and Cousins[8] concluded that human exposure to PFOA was dominated by an unknown source related to POSF-based consumer products until the 2000−2002 POSF phase-out, after which the major source of PFOA exposure will be contamination present in food items. However, the authors do not place this conclusion within the context of established temporal

trends in human sera for both PFOS and PFOA. Despite its longer half-life, PFOS is decreasing in human sera at a faster rate than PFOA (Figure 3B).[15,16,19] This implies continued exposure to PFOA without similar exposure to PFOS. For contamination present in food items to be the dominant source of current human exposure to PFOA, food-borne exposure should result in increased PFOA exposure as compared to PFOS.

Temporal data for the C9−C11 PFCAs are also included in Figure 3B. Without a distinct inflection point around the year 2000 these analytes do not follow the same trends as observed for PFHxS, PFOS, and PFOA, and as such show no apparent association with POSF production. Instead they appear to have an inflection point around 1990, with doubling times after 1990 of 79 years for PFNA, 34 years for perfluorodecanoic acid (PFDA), and a half-life of 56 years for perfluoroundecanoic acid (PFUnA) (see SI). Reasons for the disparity between temporal trends for PFNA and PFDA with PFUnA are not clear. The majority of exposure assessments have not included PFCAs aside from PFOA and so it is difficult to assess the source of human exposure to these longer chain PFCAs.[8] Biotransformation of fluorotelomer commercial products and their residuals is a possible source of PFCA exposure. This indirect exposure route is consistent with continued exposure to PFOA, PFNA, and PFDA, without similar exposure to PFOS or PFHxS.

## DIRECT HUMAN EXPOSURE SOURCES

Among direct PFA exposure sources, food has consistently been implicated as the major exposure pathway.[45−49] It has also been suggested that PFA contamination present in food items results primarily from legacy environmental contamination.[8,46] Environmental PFA contamination in often dominated by PFOS,[54] and PFOS is more bioaccumulative than PFOA.[55] However, migration from water and soil into plants is greater for PFOA as compared to PFOS.[56,57] Therefore, it is not entirely clear whether PFOS or PFOA will be dominant in food items. This is an important question, as despite its longer half-life PFOS is decreasing in human sera at a faster rate than PFOA,[15−19] and so if food-borne PFOA exposure is currently the dominant route of exposure it should result in increased exposure to PFOA relative to PFOS.

A recent study of food items from the United States observed PFOA (detects in 17 of 31 samples, 0.02−1.8 ng/g) without similar PFOS contamination, however the reported concentrations were only slightly above reported method detection limits (0.01−0.5 ng/g).[1] These results contrast a multi-city food study from the United States in 2001 where only 11 of 460 food samples had PFOA (0.54−2.3 ng/g) or PFOS (0.57−0.85 ng/g) concentrations above the method detection limit of 0.5 ng/g.[58] However, the relatively high limits of detection in this study were partially responsible for the high number of nondetects. A total diet study from the United Kingdom in 2006 observed PFOA in the potato composite only (1 ng/g) and PFOS in the potato composite (10 ng/g), eggs (1 ng/g), sugars and preserves (1 ng/g), and canned vegetables (2 ng/g).[59] The potato composite included potato chips and french fries, and so it is unclear whether the contamination was present in the potato or resulted from contact with packaging. A similar study from the United Kingdom in 2009 did not find any contamination in the potato composite, with the highest concentrations observed in oily fish (4.8 ng/g PFOS, 1.1 ng/g PFOA), shellfish (4.4 ng/g PFOS, 3.3 ng/g PFOA), and liver samples (2.5 ng/g PFOS, 1.1 ng/g PFOA).[60] A Canadian study focused on meats and packaged foods observed higher daily exposure estimates for PFOS (110 ng/day) as compared to PFOA or PFNA (both 70 ng/day).[61] A separate temporal analysis observed slightly higher intake estimates for PFOA in 1998 (0.1−0.4 ng/kg$_{bw}$/day) as compared to PFOS (0.1−0.2 ng/kg$_{bw}$/day), but this trend was reversed in 2004 with higher intake estimates for PFOS (0.8−2.0 ng/kg$_{bw}$/day) as compared to PFOA (0.1−0.4 ng/kg$_{bw}$/day).[52] A study of Spanish food items observed PFOS at low levels in the majority of the samples analyzed (20 out of 27, 0.021−0.65 ng/g); the only PFCAs detected were PFOA and PFHpA in a whole milk sample (0.056 ng/g PFOA, 0.015 ng/g PFHpA).[62] A German duplicate diet study observed slightly higher exposure estimates for PFOA (269 ng/day) as compared to PFOS (123 ng/day) in meal composites.[45] However, exposure estimates were higher for PFOS (1.5 ng/kg/day) as compared to PFOA (0.06 ng/kg/day) in Norwegian food items.[63] A Japanese duplicate diet study found very low concentrations in the meal composites, with mean concentrations of 0.03 and 0.02 ng/g for PFOS and PFOA, respectively.[47] A study of Chinese food items found similar concentrations of PFOA (0.06−12.5 ng/g) and PFOS (0.05−1.99 ng/g).[64]

Of the studies to date only three observed increased PFOA exposure as compared to PFOS in food items,[1,45,52] with the majority suggesting similar or increased exposure to PFOS.[47,58−64] Comparison between these data sets needs to be done carefully given the amount of time between the different studies and the variety of laboratories involved. However, as a whole these studies do not consistently suggest increased human exposure to PFOA relative to PFOS from food consumption. Therefore, there is likely an additional source of current PFOA exposure aside from contaminated food items. It is possible indirect exposure to fluorotelomer-based materials could account for this additional source of PFCA exposure without concerted exposure to PFOS.

Drinking water has been identified as the second most important direct exposure pathway, although its contribution is generally low in comparison to food,[46,48−50] except in locations with point-source contamination.[65,66] If drinking water has somehow been underestimated, could increasing its contribution explain increased PFOA exposure as compared to PFOS? The answer is likely no, as PFOS is often observed as the dominant species in both drinking and environmental waters.[49,50]

Direct PFA exposure obviously contributes to human exposure as PFAs are present in food, household dust, and drinking water. The pertinent question is the significance of this exposure pathway. Exposure to PFA contamination present in food and drinking water as a result of general environmental contamination is not consistent with recent temporal trends in human sera. Therefore, it seems likely there is another source of human PFA exposure that is more closely linked to fluorochemical production. As manufacturers evolve and move to different formulations the significance of direct PFA exposure will likely continue to increase.

## INDIRECT HUMAN EXPOSURE SOURCES

High concentrations of PFOS and PFOA observed in a potato composite that included french fries and potato chips suggests the contamination may have resulted from contact with food packaging.[59] PFAs are only present as contaminants in commercial products (up to $\mu$g/g levels[44,67]), and so if migration from packaging was responsible for the observed direct PFA contamination the possibility for indirect exposure via residual starting materials and commercial fluorochemicals was likely also

important. To explore the potential for indirect exposure the following discussion will present the limited data set available. In any discussion related to indirect PFA exposure it is important to appreciate that exposure is not limited to the FTOHs or PFASms (Figures 1 and 2), which are either residuals in commercial materials or their primary degradation products, but that indirect exposure also includes the commercial materials themselves (e.g., surfactants or polymers (Figures 1 and 2)). As the active ingredient, these materials are present at much higher quantities in commercial applications.

The most widely studied group of commercial fluorochemicals with respect to human exposure are the phosphate fluorosurfactants (Figures 1 and 2). These compounds are used in personal care products, as leveling and wetting agents, and as grease-proofing additives to paper food packaging.[3,44,68] Begley et al.[68] found migration of 0.4−3 $\mu$g phosphate fluorosurfactant per gram of butter after contact with treated paper packaging. These migration results agree with concentrations of the fluorotelomer mercaptoalkyl phosphate diester (FTMAP, Figure 2) observed in microwave popcorn prepared in treated packaging (1−4 $\mu$g FTMAP per gram popcorn).[68] The authors also noticed increased fluorosurfactant migration into butter, and other water−oil emulsions such as chocolate spread, than observed for any of the food simulants typically tested (water, ethanol, and oil),[68] indicating that current migration tests were underestimating fluorosurfactant exposure. Human exposure to one class of phosphate surfactants was confirmed by the observation of the 4:2 through 10:2 polyfluoroalkyl phosphate diesters (diPAPs, Figure 2) at concentrations ranging from nondetect (<0.1 $\mu$g/L) to 1.9 $\mu$g/L in human sera collected from the United States between 2004 and 2005.[69]

Aside from the investigations by Begley et al.,[44,68] there are no specific analyses looking at phosphate fluorosurfactants or any other commercial fluorochemical in food items. Tittlemier et al.[70] looked at concentrations of some residual PFSAms in food samples collected for the Canadian Total Diet Study between 1992 and 2004. The PFSAms of interest were NMeFOSA, NEtFOSA (Figure 1), and the *N*-dealkylation product perfluorooctane sulfonamide ($F(CF_2)_8SO_2NH_2$, PFOSA). The highest concentrations and frequency of detection were observed for NEtFOSA in fast food items (31 of 59 samples, 0.069−23 ng/g), which is consistent with the use of the PFSAm-based phosphate fluorosurfactants (SAmPAPs (Figure 1)) in food packaging, as both NEtFOSA and NEtFOSE are expected residuals. Yearly food samples were available from 1992 to 2004. Concentrations of NEtFOSA in fast food items decreased from the late 1990s to 2002, with no detects in 2003 or 2004. This trend is consistent with the phase-out of POSF-based materials (Figure 3A). Conversely, there was no clear decrease in the much lower concentrations of NEtFOSA observed in fish and shrimp. This difference in temporal trends likely reflects a difference in the mechanism of contamination, with the fast food samples reflecting contamination from contact with packaging, whereas the seafood samples reflect contamination through environmental sources.

PFSAm temporal trends in fast food items[70] show trends similar to PFOS in human sera.[11,15−19] The use of SAmPAPs in paper food packaging began in North America in 1974 and was discontinued with the POSF phase-out in 2000−2002.[11] Consistent with SAmPAP production, the acetate metabolite of NEtFOSE (*N*-ethyl perfluorooctane sulfonamidoacetic acid, $F(CF_2)_8SO_2N(CH_2CH_3)(CH_2C(O)OH)$, NEtFOSAA) was not observed in human sera samples from the United States collected in 1974 (<1.6 $\mu$g/L) but was present in samples from 1989 (3.4 $\mu$g/L).[11] The *N*-dealkylation product PFOSA has also been detected in human sera,[17,19,21,71] and its concentration began to decrease around the year 2000 in both Norwegian sera samples[19] and infant bloodspots from New York.[72] The similar temporal trends in NEtFOSA concentrations in fast food items,[70] with NEtFOSAA, PFOSA, and PFOS in human sera,[11,19,72] all suggest indirect exposure may be a significant source of human exposure to PFOS prior to the 2000−2002 POSF phase-out.

Studies interested in human exposure to commercial fluorochemicals have focused on the fluorosurfactants because of their applications, and physical size that facilitates absorption through the gut; however, polymeric materials are the dominant fluorochemicals produced industrially.[22] Human exposure to fluorinated polymers could occur via consumption of dust that originated from stain-protected carpet. Although the size of the polymer likely limits uptake, it is possible the ester linkage could be hydrolyzed within the gut contents releasing a smaller fluorochemical unit for absorption and further metabolism, as has been observed in microbial systems.[73] Residuals present within the polymer may also be a major contributor to this indirect exposure pathway, either via consumption of contaminated dust or inhalation of off-gassed volatile residuals such as the FTOHs and PFSAms.[25]

FTOH and PFSAm concentrations have been studied extensively in the outdoor environment, where they tend to be present at pg/m$^3$ concentrations.[74] Studies of indoor air concentrations in Canada,[75−77] Norway,[78] and Germany [79] found concentrations in the ng/m$^3$ range. The German study found unusually high concentrations of 8:2 FTOH (79−209 ng/m$^3$) and 8:2 FTAc (23−132 ng/m$^3$) at a furniture store and two outdoor equipment stores; they also observed elevated concentrations of the functional unit of the new perfluorobutyl-chemistries, *N*-methyl perfluorobutane sulfonamido ethanol ($F(CF_2)_4SO_2N(CH_3)(CH_2CH_2OH)$, NMeFBSE) (141 ng/m$^3$), at a carpet store.[79] The increased use of water- and grease-repellent materials on the merchandise sold in these stores suggests residual off-gassing from commercial products does contribute to indoor air contamination. This hypothesis was tested by Jahnke et al.[80] where indoor air FTOH and PFSAm concentrations increased by at least 1 order of magnitude when a paraglider was introduced. A study of fluorochemical exposure to ski wax technicians found extremely high indoor air FTOH concentrations (8:2 FTOH ≤ 230 000 ng/m$^3$, 10:2 FTOH ≤ 2000 ng/m$^3$),[81] as well as elevated PFCA concentrations in the blood of some of the technicians.[82]

Efforts to model human indirect exposure have focused on measurements of FTOHs and PFSAms in food, air, and drinking water. These data sets are very limited, suggesting these modeling efforts may be somewhat premature. In addition, no studies have included indirect exposure via commercial products. Given the increased production and use of commercial surfactants and polymers, relative to the FTOH or PFSAm residuals, this exposure pathway could be significant. Because of these limitations, attempts to model human indirect exposure have likely significantly underestimated its importance.

## BIOTRANSFORMATION YIELDS AND MECHANISMS

Modeling indirect human PFA exposure requires estimating human pharmacokinetic parameters and biotransformation yields. Animal models are poor predictors of human elimination,[83] and

this complicates our ability to infer human biotransformation yields as elimination kinetics are important determinants of parent and product concentrations in the body. Difficulties aside, there is significant knowledge available regarding the fate of PFAs and their precursors in biological systems.

Biotransformation of the PFSAms has been studied using either NEtFOSE or NEtFOSA and generally proceeds via consumption of the alkylamine moiety leaving PFOS as the final stable product (see SI).[26−29] FTOH biotransformation proceeds via a $\beta$-oxidation-like mechanism, producing the PFCA two carbon units shorter than the parent FTOH as the major PFCA oxidation product (e.g., 8:2 FTOH to PFOA) (see SI).[30−34] It has been speculated that the FTOHs cannot proceed via true enzymatic $\beta$-oxidation as this would involve transfer of a fluorine atom to the cofactor flavin adenine dinucleotide (FAD), something that would not be energetically favorable.[84] Unlike the PFSAms, there is no sulfonate barrier between the FTOH hydrocarbon moiety and its fluorinated tail. This provides a mechanism for transformation of the fluorinated moiety, and so although FTOH biotransformation is dominated by the $\beta$-oxidation product a range of PFCAs is produced. This difference also changes the nature of the metabolic intermediates, which in FTOH biotransformation include electrophilic species such as unsaturated fluorinated aldehydes.[32,85,86]

Biotransformation yields from NEtFOSE or NEtFOSA to PFOS in cellular incubations have generally been low (<1%),[26,28,29] with numerous other primary oxidation products and secondary metabolites produced. However, the yield of NEtFOSE to PFOS in the rat is increased significantly to around 20% (42.5 $\mu$g/mL PFOS in serum after 21-day daily gavage dosing at 5 mg/kg NEtFOSE (see SI)).[27] Conversely, the yield of PFOA from 8:2 FTOH biotransformation has generally been low in both cellular incubations[30−33] and rats (0.8% yield from 1.61 $\mu$g/mL PFOA in rat plasma after 45-day daily gavage dosing at 5 mg/kg 8:2 FTOH (see SI)).[34] How to apply the biotransformation yields determined in rats to humans is not entirely clear as the larger NEtFOSE to PFOS yields as compared to 8:2 FTOH to PFOA are driven at least in part by the marked difference in PFOS and PFOA serum elimination half-lives in rats (30 days for PFOS, 5−15 days for PFOA in male rats[83]) that are not as pronounced in humans (5.4 years for PFOS, 3.8 years for PFOA[51]).

The only thorough pharmacokinetic evaluation of a commercial fluorochemical was performed on the diPAPs. Exposure to the 4:2, 6:2, 8:2, and 10:2 diPAP congeners in the rat resulted in biotransformation yields of 1% for 6:2 diPAP (to perfluorohexanoic acid (PFHxA)), 9% for 8:2 diPAP (to PFOA), and 8% for 10:2 diPAP (to PFDA).[7] Unlike the FTOH and PFSAm biotransformation yields described above, which were determined using blood versus dose concentrations,[27,34] these diPAP biotransformation yields were determined using the relative area under the concentration−time curves for the parent and product compounds (see SI).[7] This simplifies exposure modeling if parent concentrations have been measured in human sera, as it does not rely on measurements in exposure media or estimates of chemical migration and uptake. The diPAP biotransformation yields were used to calculate PFOA exposure from 8:2 diPAP observed in human sera (0.15 $\mu$g/L[69]), and indicated that over time low level exposure to a commercial fluorotelomer-based material, such as the diPAPs, could explain continued PFCA exposure.[7]

Two studies have attempted to model exposure to direct and indirect PFA sources, and both found direct exposure via

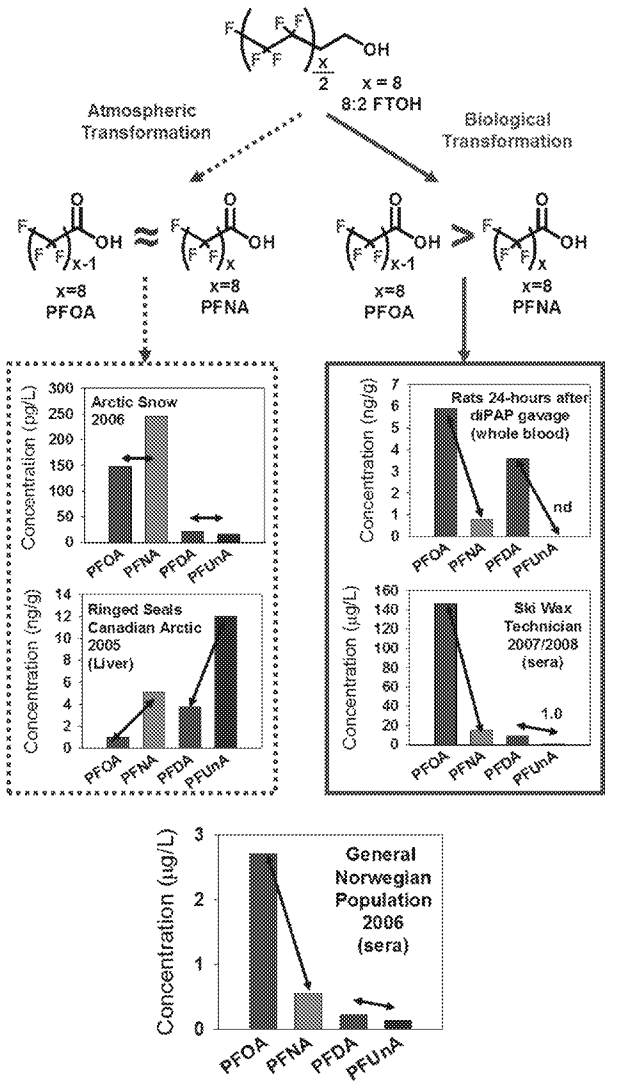


**Figure 4.** Examples of the PFCA congener profile observed in samples where the dominant PFCA source is suspected to be fluorotelomer alcohol (FTOH) atmospheric oxidation (Arctic snow, 50 cm depth,[91] Ringed Seals, Arviat[94]), or FTOH biotransformation (diPAP-exposed rats,[7] ski wax technician 3 during world cup season[82]), together with the PFCA congener profile observed in the general Norwegian population in 2006.[19] Black arrows reflect trends in PFCA congener pairs (PFOA/PFNA and PFDA/PFUnA) that may reflect the indirect source of this contamination.

contamination food items to be the major source of human exposure.[48,49] Biotransformation yields used in these studies ranged from 0.02% to 5% for 8:2 FTOH to PFOA and 10% to 100% for PFSAm to PFOS. Aside from appropriate pharmacokinetic parameters, predicted exposure from indirect sources was significantly underestimated in both studies as only residual materials were considered and not exposure to the commercial products themselves, which are likely present at much higher levels.[44,68] In the interest of characterizing human exposure it may be more important to obtain accurate exposure estimates to commercial materials and their residuals, as opposed to further refining biotransformation parameters, as even very low biotransformation yields could result in significant indirect PFA exposure if exposure to these materials was high enough.

Ski wax technicians exposed to very high indoor air FTOH concentrations (8:2 FTOH ≤ 230 000 ng/m$^3$, 10:2 FTOH ≤ 2000 ng/m$^3$ [81]) have PFCA congener profiles in their sera that are suggestive of FTOH biotransformation (Figure 4), with the dominance of even-chain PFCA congeners as compared to odd (e.g., PFOA > PFNA).[32,33] A similar PFCA congener profile was observed in rats 24 h after a bolus gavage dose of a diPAP mixture.[7] The PFCA congener profile of samples from the general Norwegian population is also shown in Figure 4, and the profile is relatively similar to that observed in the ski wax technicians. This similarity is consistent with some contribution from indirect fluorotelomer exposure to the PFCAs observed in the Norwegian samples. The isomer profile of PFOA in human sera from the United States is also consistent with a fluorotelomer-based exposure source, as it is also almost entirely linear (97% linear as compared to 80% in ECF PFOA),[87] with decreased contribution from specific ECF isomers that were found to be more bioaccumulative than the linear isomer in rats.[88,89]

The PFCA congener profile in the ski wax technicians contrasts that observed from FTOH atmospheric oxidation, which produces similar concentrations of the PFCA pairs (e.g., PFOA = PFNA from 8:2 FTOH).[90] These experimental atmospheric yields were consistent with similar concentrations of the atmospherically derived PFCA pairs PFOA/PFNA and PFDA/PFUnA observed in Arctic snow (Figure 4),[91] which may explain the dominance of the odd-chain PFCA congeners in Arctic biota that may be driven by increased bioaccumulation of the longer odd-chain congener (Figure 4).[92−94]

## CONCLUSION REGARDING DIRECT VERSUS INDIRECT HUMAN EXPOSURE

As the active ingredient, commercial fluorochemicals represent the largest burden of fluorochemicals in the indoor environment. Despite this potential for exposure, we know very little about their fate, migration, uptake, biotransformation, or elimination. This is a large data gap. Total organofluorine analysis of human sera indicates that only 30−70% of the organofluorine present in human sera can be identified by known PFAs.[95] Without a better understanding of human exposure to commercial materials it may not be possible to fully understand human fluorochemical exposure.

Temporal trends in human sera suggest current-use POSF-based commercial products were a significant source of human exposure to PFOS prior to the 2000−2002 POSF phase-out (Figure 3).[11,15−19] Similarities between the temporal trends observed in human sera for PFOS and those for the PFSAm metabolite PFOSA[19,72] suggest indirect exposure via PFSAm biotransformation may have been important in the observed PFOS contamination. PFOS and PFOSA trends in human sera are also similar to the temporal trend of the residual NEtFOSA in fast food items,[70] providing a connection between human sera contamination and a potential exposure source (exposure to the NEtFOSA and NEtFOSE residuals, as well as the SAmPAP commercial product). Human exposure models have suggested direct PFOS exposure via contaminated food items is the major exposure pathway.[45−49] Contamination present in food items does contribute to PFOS exposure, and this exposure source may dominate once PFOS from POSF-related materials has depurated, but considering the changes observed in human sera were not observed in a temporal analysis of PFAs in food items[52] this exposure pathway was not dominant prior to the 2000−2002 POSF phase-out.

Similar to PFOS, PFOA began to decrease in human sera starting around the year 2000 (Figure 3B).[11,15−19] Conversely, the concentrations of PFNA and PFDA have continued to increase.[16,19] These trends indicate that prior to 2000 there was a source of human exposure to PFOA independent of the other PFCAs. A possible explanation for this distinct PFOA source is that, similar to PFOS, it was related to current-use POSF-based commercial materials. The relatively long half-life for PFOA in the temporal data sets[15−19] indicates there is an additional source of human exposure to PFOA aside from that potentially related to POSF production, which may be connected to the other PFCAs. Indirect exposure via fluorotelomer-based commercial products or residuals could explain continued exposure to PFOA, together with exposure to PFNA and PFDA, without similar exposure to PFOS. Conversely, it is difficult to explain these temporal trends using PFA contamination present in food items, as PFOS is often present at concentrations similar to PFOA.[1,45,47,52,58−64]

Human PFA exposure involves a combination of direct and indirect sources; the difficulty lies in determining the relative importance of these sources. There is no single piece of evidence which points unequivocally at the dominance of one exposure source over the other, but when considered as a whole the data set is generally consistent with indirect exposure representing a significant source of the observed human PFA contamination.

Further studies are necessary to expand the data set on commercial fluorochemicals and residuals in exposure media, as the magnitude of human exposure to these materials remains poorly understood. The significance of indirect versus direct human exposure has important regulatory implications, as the two exposure pathways are very different both toxicologically and with respect to appropriate mechanisms to control human exposure. Direct exposure to legacy environmental contamination may be difficult to avoid, whereas regulatory efforts could potentially be very effective at controlling indirect exposure to current-use commercial materials. Limiting indirect exposure may be especially important as electrophilic metabolites have been identified in the metabolism from FTOH to PFCA[32,85,86] and so there is potential for toxicity associated specifically with the indirect route of exposure.

## ASSOCIATED CONTENT

**Supporting Information.** Additional text, references, and figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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